Exhibit D

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ARIOSA DIAGNOSTICS
Petitioner

v.

ISIS INNOVATION LIMITED
Patent Owner

CASE IPR2013-00250
Patent 6,258,540

ISIS INNOVATION LIMITED'S PRELIMINARY RESPONSE
37 C.F.R. §42.120

I. Introduction

Ariosa's Petition should be denied because it is premised on a faulty claim construction, did not establish a reasonable likelihood of prevailing on any proposed ground of unpatentability, and is statutorily barred.

The Board should not institute *inter partes* review because Ariosa has not met its burden to show it has a reasonable likelihood of prevailing on any of its proposed grounds of unpatentability. Ariosa's arguments hinge on a faulty claim construction and a disregard for (i) the extensive literature teaching away from the invention and (ii) the objective indicia of nonobviousness. Additionally, the petition should be denied because Ariosa lacks standing to petition for IPR in view of (i) its prior district-court challenge to the validity of the '540 patent and (ii) the fact that Ariosa was served with a complaint alleging infringement of the '540 patent more than a year ago. And even if the Board institutes review, Ariosa's proposed grounds of unpatentability against claim 8 should be denied because the same art and arguments previously were presented to the Office.

II. Ariosa's petition is premised on a faulty claim construction.

Ariosa's petition is premised on a faulty claim construction that disregards the intrinsic evidence. Ariosa thus arrives at an *unreasonably* broad construction upon which Ariosa relies to assert unpatentability. But Ariosa's argument must fail because it is contradicted by the evidence.

A. The "detecting" clause of the independent claims requires distinguishing fetal nucleic acid from that of the mother.

Ariosa argues that the claims do not require "detecting" paternally inherited nucleic acid of fetal origin:

> In claim 1, the step 'detecting the presence of a paternally inherited nucleic acid from the serum or plasma sample' was interpreted as not requiring 'that the nucleic acid be specifically identified as being inherited from the father or even as being from the fetus, only that it be identified as containing some level of nucleic acid.'

2nd Pet. at 19. In other words, Ariosa asserts that the presence of this nucleic acid need not be appreciated. But this interpretation would render the claims meaningless because the method then wouldn't tell one anything about the fetus or the condition of the mother. So Ariosa's construction is at odds with the whole nature of the disclosed invention.

And the intrinsic evidence shows that "detecting" the presence of a paternally inherited nucleic acid of fetal origin requires *appreciating* that the nucleic acid is fetal and is inherited from the father.

B. All of the '540 patent's examples appreciate the existence of paternally inherited fetal DNA.

The claims should be construed in light of the specification. But the analysis should begin with the plain language of the claims. By suggesting that the claims

do not require one to appreciate that the detected nucleic acid is "paternally inherited nucleic acid of fetal origin," Ariosa contradicts the words of the claims themselves and the entire intrinsic record.

All of the specification's examples require *appreciating* that the amplified fetal DNA is paternally inherited, i.e., not inherited from the mother. In the Detailed Description, which was included in the GB priority application, the specification describes several exemplary methods that all require appreciating that the fetal nucleic is paternally inherited. In introducing these examples, the specification states:

> The method according to the invention can be applied to the detection of any paternally-inherited sequences which are not possessed by the mother and which may be for example genes which confer a disease phenotype in the foetus.

The '540 patent at 2:57-61. The specification then describes several types of nucleic acid testing: all require appreciating that the nucleic acid is paternally-inherited. The first example is RhD status. This test is irrelevant if the mother is RhD positive. It is only when the mother is RhD negative, and could develop antibodies against the fetus, that the RhD status of the fetus is at issue. So the first example requires appreciating that the RhD status of the fetus is positive, i.e., paternally-inherited, relative to the mother's status.

Likewise, the next example describes the many known hemoglobinopathies, and also requires appreciating that the fetal nucleic acid is paternally-inherited. The '540 patent at 3:6-10 states: "Provided that the father and mother carry *different* mutations, the paternal mutation can be used as an amplification target on maternal plasma and serum, so as to assess the risk that the foetus may be affected." (emphasis added). This example thus relies on appreciating that one has detected paternally-inherited nucleic acid of fetal origin.

And the third example requires appreciating that the fetal DNA is paternally-inherited: "Paternally-inherited DNA polymorphisms or mutations present on either a Y or a non-Y chromosome, can be detected in maternal plasma and serum to assess the risk of the foetus being affected by a particular disease by linkage analysis." The '540 patent at 3:11-16. In a further illustration of this example, the parents are genotyped before testing and "an allele for detection will be chosen which is present in the father, but is absent in the mother." Id. at 3:20-24.

The next two examples, and the first working example, all of which were included in the GB priority application, also require that the presence or fact of the paternally inherited nucleic acid is appreciated. Detecting fetal aneuploidy by quantitating either total fetal DNA or fetal DNA markers on different chromosomes requires an appreciation of the fetal DNA, i.e., the fact that it differs from maternal DNA. Likewise, sex determination of a male fetus, as in the first

working example, requires that the presence of the Y chromosome be determined.

The following working examples also require that the fact or presence of paternally inherited fetal nucleic acid be appreciated. These examples include data for quantitative and non-quantitative methods, as is discussed above.

In sum, every example in the '540 patent requires that the presence of paternally-inherited fetal nucleic acid be *appreciated*. The invention does not make sense otherwise. The broadest reasonable interpretation thus must give weight to "detecting" this nucleic acid. And Ariosa is therefore wrong in stating that the claims do not require distinguishing the fetal nucleic acid from maternal nucleic acid.

C. The prosecution history shows that detecting paternally inherited fetal nucleic acid requires distinguishing it from maternal nucleic acid.

The intrinsic evidence also includes the prosecution history, which like the specification, shows that the presence of paternally inherited nucleic acid must be appreciated. This history includes amendments by the Patentees and the Examiner.

1. "Paternally inherited" was added to the claims.

First, in response to an enablement rejection, the Patentees amended claim 1 to add "paternally inherited" to the detecting step, as follows: "detecting the presence of a paternally inherited nucleic acid of fetal origin." 12/27/2000 Response (EX2054) at 2-3. And they amended claim 26, which became patent

claim 25, to add "to detect paternally inherited fetal nucleic acid." *Id*.

Second, an Examiner's amendment added, after the "subjecting … to a test" phrase, the language "for the paternally inherited fetal nucleic acid" to claims 25, which became patent claim 24. Notice of Allowability (EX2055) at 2-3.

The claims thus require the paternally inherited fetal nucleic acid to be appreciated.

2. The "amplifying" step was also added and must be given separate meaning from the detecting step.

Third, the Examiner added the "amplifying" step to patent claims 1, 25, and 26 before allowing the claims. Notice of Allowability (EX2055) at 2-3. Amplifying is thus not the same as detecting.

Under Ariosa's unreasonably broad interpretation, however, "amplifying" the paternally-inherited nucleic acid of fetal origin also meets the "detecting" limitation. And Ariosa's proposed Ground G that claim 8 is anticipated by Kazakov requires this broad interpretation. When the claims are given their proper, reasonably broad construction—giving meaning to both steps—then Kazakov fails to meet at least the "detecting" step.

D. Federal Circuit jurisprudence supports reliance on the intrinsic evidence over any alleged extrinsic evidence.

The intrinsic evidence is clear. It would be error in this case to rely on extrinsic evidence that contradicts the intrinsic evidence. *Phillips v. AWH Corp*.,

415 F.3d 1303 at 1318 (Fed. Cir. 2005). *Phillips* states that extrinsic evidence cannot be relied on if it contradicts the intrinsic evidence: "[A] court should discount any expert testimony 'that is clearly at odds with the claim construction mandated by the claims themselves, the written description, and the prosecution history, in other words, with the written record of the patent.'" To the extent the Board views the testimony of any witness as being contradicted by the intrinsic evidence, the intrinsic evidence should control.

III. The '540 patent is entitled to its GB priority application filing date—the scope of "fetal" and "fetus" did not change.

Ariosa argues that the scope of the terms "fetal" and "fetus" changed between the GB priority filing date and the '540 patent filing date. Specifically, Ariosa's position is that the specification's change from "12 to 40 weeks of gestation" in the earlier application to "7 to 40 weeks of gestation" in the patent changed the definition of these terms.[1] The changed phrase appears as follows:

> It is anticipated that it will be possible to incorporate the nucleic acid-based diagnosis methods described herein into existing prenatal screening programmes. Sex

[1] Persons of ordinary skill in the art (POSAs) of fetal nucleic acid testing counted pregnancy in "gestation" weeks starting with the first day of the pregnant woman's last menstrual period (LMP). The LMP thus generally occurs about two weeks prior to fertilization.

> determination has successfully been performed on pregnancies from **[12]** 7 to 40 weeks of gestation.

EX1004 at 6:3-6; EX1001 at 3:58-62 (amendment noted; emphasis added). Ariosa also provided Robbins, a pathology text, to argue that the "fetal" portion of human development begins after week 8 (the beginning of week 9 of pregnancy).

But the scope of the terms fetal and fetus in the claims did not change: (a) the terms are meant to designate the DNA source (e.g., non-maternal) rather than impose a certain age requirement on the fetus; (b) the changed language in the specification merely provides disclosure for additional working examples, which do not limit the scope of the claims; (c) the inventors did not act as their own lexicographers, so the ordinary and customary meanings of "fetal" and "fetus" control; (d) the plain and ordinary meaning of these terms encompasses gestation week 7; and (e) the GB priority application and the '540 patent use these terms consistently with their meanings in the art.

A. The word "fetal" in the independent claims modifies nucleic acid and is intended to describe the source of the DNA, not impose an age limit on when the claimed method can be performed.

The independent claims of the '540 patent are claims 1, 21, 24 and 25. None of these claims uses the term "fetus." Claim 1 uses the term "nucleic acid of fetal origin." Claim 21 uses the term "nucleic acid of foetal origin." Claims 24 and 25 both use the term "fetal nucleic acid." In each of these claims, the term fetal is

used to modify "nucleic acid" so as to distinguish it, based on source, from maternal nucleic acid. That is the only limitation placed on the independent claims of the '540 patent by use of the word fetal.

Conversely, the amendment complained of by Ariosa, which changes 12 to a 7, does not involve the word fetal, or occur in a sentence in the specification that uses the word fetal. The most ordinary meaning attributable to this amendment is that, as of the original application filing date, sex determination had been performed successfully on pregnancies from 12 to 40 weeks of gestation. At the second filing date, this sentence was updated to reflect that sex determination had been performed successfully on pregnancies from 7 to 40 weeks of gestation. Note that this statement does not define, nor does it attempt to define, the gestational age boundaries that define a fetus.

B. The working examples do not limit the claims.

The change from 12 to 7 weeks in the '540 patent merely summarizes the working examples, which do not limit the claims. See *DealerTrack, Inc. v. Huber*, 674 F.3d 1315, 1322 (Fed. Cir. 2012). Here, Example 1, which was present in the GB priority application, contained experimental data from gestation weeks 12 to 40. Example 5, which was added at the March 4, 1998 filing date, contained experimental data from gestation weeks 7 to 40. To reflect the new data, the applicants changed a single sentence in the Detailed Description: "Sex

determination has successfully been performed on pregnancies from [12] 7 to 40 weeks of gestation."

Neither that sentence nor any of the examples defines the term "fetal." Indeed, not one part of the '540 patent (or the GB priority application) defines the term "fetal."

And here, not only are the Examples clearly identified as such, but the specification explicitly states that the Examples "do not in any way limit the scope of the invention." EX1001 at 4:10-14. *See Aventis Pharma v.Apotex Inc.*, 675 F.3d 1324, 1330 (Fed. Cir. 2012) (noting that the specification in question "expressly instructs that the disclosed examples 'are not to be considered as limiting the invention.'"). The Federal Circuit has cautioned: "[A]though the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments." *Phillips* at 1323. Yet that is precisely what Ariosa seeks to do.

The "12 to 40" and "7 to 40" time frames mentioned in the specifications thus do not define the term "fetal" or "fetus."

C. The inventors did not redefine the term "fetal" or "fetus."

Here, the inventors did not act as their own lexicographers: Neither the '540 patent nor the GB priority application defines "fetal."

To act as his own lexicographer, a patentee "must 'clearly express an intent

to *redefine* the term.'" *Aventis Pharma* at 1330 (emphasis added). Here, the inventors did not express any intent to redefine "fetal" or "fetus." As discussed above, the relied-upon sentence merely summarizes the working examples. So the ordinary and customary meaning applies. *Id*. And, as will be discussed below, the GB priority application's use of "fetal" and "fetus" as encompassing gestation week 7 is consistent with the art of fetal testing. Thus, the inventors did not redefine these terms.

D. "Fetal" and "fetus" ordinarily and customarily encompass gestation week 7.

The ordinary and customary meanings of "fetal" and "fetus" encompass gestation week 7. Notably, if the definition of fetal in the prior art encompassed *only* gestation weeks 12 to 40, then references discussing *earlier* gestational weeks ordinarily and customarily would have used the terms "embryo" and "embryonic" for those earlier weeks—but they did not. For example, Simpson (EX1024) discusses gestation weeks 10 and 11. EX1024 at 2358:3:¶2, 2359:Table, 2360:1:¶3 & 2:¶2. Simpson 1994 (EX1025) discusses gestation weeks 6 to 10. EX1025 at 1237:2:Table IV. But Simpson never used the words "embryo" or "embryonic." EX1024, throughout; EX1025, throughout. In fact, the prior art ordinarily and customarily reserved the terms "embryo" and "embryonic" for discussing pre-implantation genetics, i.e., genetic testing performed on in vitro embryos rather

than testing done on pregnant women.[2] The '540 patent and GB application are thus consistent with the usage of fetal and fetus (and embryo and embryonic) in the art.

1. Extrinsic evidence shows that POSAs used the term "fetal" and "fetus" as broadly as the GB application uses them.

In the absence of an express definition, a term has its ordinary meaning, which "must be determined from the standpoint of a person of ordinary skill in the relevant art." *Teleflex* at 1325. The fetal testing field has included gestation week 7 within the scope of "fetal" and "fetus" since at least 1972. E.g., Robinson 1972 (describing the ultrasound detection of "fetal" heart movement at gestation day 48, which is one day shy of gestation week 7). EX2056. A significant body of evidence, which is discussed below, supports this conclusion.

The prior art shows how the terms "fetal" and "fetus" would have been understood in the art and confirms that gestation weeks earlier than 12 were within the scope of these terms. Extrinsic evidence "can help the court determine what a person of ordinary skill in the art would understand claim terms to mean." *Phillips* at 1319.

For example, the attached exemplary 12 prior art abstracts describe testing performed on "fetal" samples at a time earlier than gestation week 12. Sherer;

[2] Adinolfi (EX2058); Edwards and Hollands (EX2059); Hardy (EX2060).

Sekizawa; van Wijk, Durrant; Massari; Reading; Von Koskull; Nicolaides; Hobbins; Voigt; Lanlois; and Youssef (collectively, EX2057).

And even Ariosa's cited references include gestation week 7 in the term "fetal." For example, the Simpson 1994 reference included weeks 6-10 as "fetal." EX1025 at 1237:2:Table IV. And Simpson 1994 used the term "fetal" (or variants of fetal) more than 100 times to refer to weeks 6-10 Likewise, Lo 1990 included gestation weeks 6-41 as "fetal." EX1044 at 1463:2 & 1463:2:Table. Thus, even the evidence Ariosa cited contradicts its argument that 7 weeks is considered "embryonic" rather than "fetal."

In contrast, the prior art ordinarily and customarily reserved the terms embryo and embryonic for pre-implantation genetic testing, e.g., testing performed on embryos created by in vitro fertilization prior to transfer to the woman.

The extrinsic evidence thus weighs heavily in favor of the ordinary and customary meaning of fetal and fetus as including gestational weeks before week 12.

2. The '540 patent and the GB application use the terms "fetal" and "fetus" consistently with the meaning in the art—these terms encompass gestation week 7.

Both the GB priority application and the '540 patent use the term "fetal" and "fetus" consistently with the way these terms were used in the art. They encompass gestation week 7.

For example, both specifications discuss then-current screening programs that included chorionic villus sampling (CVS): "*Conventional prenatal screening methods* for detecting *foetal* abnormalities and for sex determination traditionally use *foetal* samples derived by … chorionic villus sampling."[3] Both specifications further state that the invention could be *incorporated into* "existing prenatal screening programmes."[4] CVS was being performed on fetuses earlier than gestation week 12.[5,6] ***Thus, the GB priority application expressly indicates that the invention could be performed at the same gestational stages as then-current screening technology—including at gestation week 7***.

And both specifications cite publications in their background sections that use fetal and fetus as encompassing gestation weeks earlier than 12. In particular,

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[3] EX1004 at 1:7-10; EX1001 at 1:12-15 (emphasis added).

[4] EX1004 at 6:3-5; EX1001 at 3:58-60.

[5] See WO 91/08304 (cited in both specifications and describing CVS being performed at gestation week 6) (EX2061); Jackson (1992) (EX2062) (describing CVS being performed on fetuses at gestation weeks 7-12).

[6] EX1004 at 5:7-10, 11-15, 16-18 & 19-23; EX1001 at 3:30-34, 34-40, 43, 44-45 & 45-49 (both specifications citing identical publications that test "fetal" samples at 10 and 9 weeks).

WO 91/08304 determined "fetal" sex at gestation week 6:

> We have used this system on a series of 37 pregnant women, with gestational ages ranging from ***6*** to 41 weeks (see Table 2). Early pregnancy samples (6- 11 weeks) were obtained from women under investigation for prenatal diagnosis of possible genetic disorders at the University of Milan. Blood samples were taken before chorionic villus biopsy and the sex of the *foetus* was determined from cytogenic analysis of chorionic villus culture.

WO 91/08304 (EX2061) at 19:4-12 (emphasis added).[7,8] In the 1st IPR, the Board's construction of the term "fetal" in the GB application as beginning at 12 weeks is

[7] For purposes of claim construction, prior art cited during prosecution is part of the intrinsic record. *Phillips* at 1317. WO 91/08304 was cited during prosecution. '540 patent at face page ("References Cited").

[8] Also see the following publications cited in the '540 background section: Cheung (1996) (EX2007) (describing fetal cells collected from pregnant women at 10 weeks gestation.) at 267:2:¶2; Lo (1989) (EX1014) (determined fetal sex from maternal blood at 9 weeks gestation) at 1363:2:¶3 & 1364:2:¶1; Simpson (1993) (EX1024) (analyzed maternal blood from samples at gestation week 10) at 2359:Table & 2360:1:¶3.

therefore contradicted by intrinsic evidence, including the GB application itself.[9]

IV. Under both the proper and the erroneous construction for the "detecting" step, Kazakov does not anticipate claim 8 expressly or inherently.

A. Under the proper claim construction, Kazakov does not meet all of claim 8's limitations because it fails to teach the *detecting* step.

When the claims are given their proper, broadest *reasonable* construction,

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[9] The Kazakov Declaration alleged that the change from gestation week 12 to 7 was significant because "fetal DNA" is "substantially more abundant" before week 12, thus making earlier testing "substantially more effective." EX 1006 at ¶¶73. But this is factually wrong about fetal *cell free* DNA. To support this argument, the Kazakov Declaration cited Smid 1997. EX 1006 at ¶73, citing EX2063. But Smid 1997 measured fetal *cellular* DNA, not fetal *cell free* DNA: it used DNA extracted from whole blood. EX2063 at 1518:1:¶3. Smid 1999 confirms that this is true. EX 2064 at 1570:1:¶3. Fetal cell free DNA, on the other hand, does not decrease after week 12. Smid 1999 (EX2064) at 1571:2:¶1. Smid 1999 acknowledges this when it states that fetal cellular DNA disappears in the second trimester, but that fetal cell free DNA does not. Id.; Jorgez 2009 (EX2065) at 314:2:¶2.

Therefore, Kazakov's testimony is irrelevant to the significance of the scope of "fetal" and "fetus" as applied to the '540 patent claims.

Kazakov does not expressly or inherently anticipate claim 8.

Ariosa's attack on claim 8 as being anticipated by Kazakov depends on an erroneous claim interpretation that does not require *appreciating* the paternally-inherited fetal nucleic acid. It's remarkable that Ariosa alleges Kazakov carried out the claimed subject matter first—he had zero ability to distinguish paternally-inherited fetal DNA from the mother's, let alone to carry out prenatal diagnosis. And numerous post-filing date publications credit Drs. Lo and Wainscoat with making the inventive jump that no one else made that lead to the invention. Bianchi 1998 (EX2071); Smid 1999 (EX2064). Can Kazakov make this claim? No: Kazakov admitted that he did not disclose detecting paternally inherited nucleic acid of fetal origin. EX 1006 at ¶21; EX 1046 at ¶23 (These exhibits are declarations by the first author of Kazakov).

Because the claims as properly construed require that the presence of paternally inherited fetal nucleic acid is *appreciated*, Kazakov failed to meet all the claim limitations.

B. Even under Ariosa's erroneous construction, Kazakov does not meet all of claim 8's limitations.

But even under the Ariosa's erroneous construction, Kazakov also fails to meet all of claim 8's limitations because it fails to teach its amplifying step. Kazakov only amplified a single Alu fragment using the B1/C2 primers. But

Ariosa asserts and provides evidence allegedly showing that Kazakov amplified multiple chromosomes, including the Y chromosome, using these primers. Ariosa thus cannot establish that the fragment amplified by these primers was necessarily from the non-Y chromosome, as claim 8 requires.

1. Using the B1/C2 primers, Kazakov amplified only one Alu fragment, and thus did *not* necessarily amplify the non-Y chromosome recited in claim 8.

The Board previously found that "it is unclear what was amplified by the B1 and C2 primers described in the Kazakov reference." Decision at 26. It is *still unclear* what these primers amplified.

Ariosa asserts that Kazakov's B1 and C2 primers amplified sequences on Y and multiple non-Y chromosomes. 2nd Pet. at 3:¶1; EX 1046 at ¶28. But Kazakov only amplified a single product using the B1 and C2 primers: "When the PCR was carried out with the pair of primers B1 and C2, *an Alu repeat* … was amplified…." EX 1014 at 233:¶6 (emphasis added) & Inset VIII:Fig. 1.

Claim 8 requires detection of fetal nucleic acid from a paternally-inherited non-Y chromosome. Because Kazakov produced only a single product, he cannot have *necessarily* amplified the Alu sequences on each and every chromosome alleged by Ariosa to have been amplified. Since the single amplified Alu sequence could have been from the Y chromosome—and Ariosa argues that it is (2nd Pet. at 3:¶1)—Kazakov does not inherently anticipate claim 8.

Under the inherency doctrine, mere probabilities are insufficient to establish that a reference anticipates. Ariosa's new "evidence" casts even more doubt than before on its inherency position.

2. Kazakov did not detect, or inherently amplify, *fetal* cell free DNA.

And even if serum inherently contains fetal cell free DNA, that does not mean that Kazakov inherently *amplified* or *detected* it because maternal nucleic acid *alone* may have been detected.

Evidence that Kazakov did not necessarily amplify fetal cell free comes from the fact that Kazakov detected *no* amplification products when using the Tc65 primer to amplify serum of women with preeclampsia. EX 1014 at 233:¶3 (reporting that only first trimester samples were positive for Tc65 amplification). But fetal cell free DNA levels rise *86-fold* during preeclampsia. Lazar 2009 (EX 2066) at 5:2:¶2. In contrast, total cell free DNA rises only 2.85 fold. *Id*. So any potential swamping-out effect that the maternal DNA might have had on amplifying fetal DNA would have been eliminated in these samples if Kazakov's samples had contained fetal cell free DNA.

If Kazakov had necessarily amplified *fetal* cell free DNA, the pre-eclampsia samples would have been positive for Tc65 amplification. But they were not, and Kazakov therefore did *not* amplify fetal cell free DNA.

For at least this reason, Ariosa's evidence is legally and scientifically insufficient to show that Kazakov necessarily amplified fetal cell free DNA. Ariosa thus is not reasonably likely to prevail in showing that Kazakov anticipates claim 8 (or any other claim).

V. When "fetal" and "fetus" are correctly construed, the '540 patent is entitled to its earliest filing date, eliminating Lo 1997 and Schallhammer as prior art.

Because the definitions of "fetal" and "fetus" didn't change between filing the GB and US applications, the '540 patent is entitled to its earliest priority date. Since Lo 1997 (EX1016) and Schallhammer (EX2035) are intervening, they are eliminated as "prior" art. As Ariosa's proposed Grounds C-F are based on at least one of these references, Ariosa is not reasonably likely to prevail as to any of these grounds. 2nd Pet. at iii & 38-53.

VI. None of the references identified in the proposed grounds of unpatentability anticipates or renders obvious the claims.

A. Ariosa is not reasonably likely to prevail on its proposed Ground A.

Ariosa is not reasonably likely to prevail on its proposed Ground A. Claims 3, 12, 13, 15, and 18 are nonobvious over Kazakov in view of Bianchi because (a) Ariosa failed to show a prima facie case because there was no reasonable expectation of successfully detecting fetal nucleic acid in serum or plasma, (b) the art taught away from using serum or plasma to detect fetal nucleic acid, and (c)

substantial objective evidence weighs heavily in favor of nonobviousness.

1. Ariosa mischaracterizes the state of the art.

Ariosa misstated several material facts that form the bases for some of its proposed unpatentability grounds. Isis makes the following corrections.

a) It was known that fetal cells in maternal blood were *rare*.

Ariosa alleges that it was widely known that fetal cells in maternal circulation could be isolated and tested. The implication of this allegation is that fetal cells would be abundant. Coupled with a second Ariosa allegation (that fetal cells would be recognized as foreign and would be killed by the mother's immune system, releasing fetal DNA into the mother's circulation), Ariosa implies that fetal cell free DNA would have been expected in maternal blood.

But Ariosa (a) ignores the multitude of prior art publications expressing skepticism about isolating and testing these cells due to their extraordinary rarity, and (b) ignores the multitude of post filing date publications praising the success of '540 patent's invention. This rarity, skepticism, and praise are discussed in Section VI(B), below.

b) POSAs would *not* have expected maternal peripheral NK cells to have destroyed fetal trophoblasts.

Ariosa alleges that it was expected that cells of the mother's immune system would destroy fetal cells that escaped into maternal circulation because these

immune cells would recognize the fetal cells as foreign. But this too is false.

Ariosa's proposed grounds for obviousness hinge on this faulty allegation in combination with the false implication that fetal cells were abundant in maternal blood. Ariosa specifically alleges that fetal trophoblast cells that escaped into the mother's general circulation would be expected to be recognized as foreign or "non-self" by the mother's peripheral natural killer (NK) cells and would be destroyed, thereby releasing fetal cell free DNA. Ariosa bases this allegation on references that allegedly describe uterine NK cells as being less cytotoxic than their peripheral blood counterparts.

But, contrary to Ariosa's position, POSAs knew by March 1997 that fetal trophoblasts would not be recognized by peripheral NK cells as "non-self" because trophoblasts express proteins on their surface that protect against killing by NK cells (HLA-C and -G antigens). Hunt 1992 (EX2087) at abstract (fetal trophoblasts express HLA-G); Pazmany 1996 (EX2067) at abstract (showing that NK target cells transfected with HLA-G were protected from killing by peripheral blood NK cells from several donors); Crisa 1997 (EX 2068) at abstract, 289:2:¶1, 295:2:¶2 to 296:1:¶2 (citing pre-filing date articles); Chumbley 1994 (EX2069) at ¶ spanning 317-318 (multiple trophoblast types strongly express HLA-G).

And Ariosa relies on Ho for the idea that uterine NK cells are less cytotoxic to fetal cells than are peripheral NK cells, but Ho doesn't use fetal cells to test

cytotoxicity. Ho (EX 1013) at 131:2:¶3. Ho uses a *leukemia* cell line (K562). *Id*.; EX 2070 at abstract. And Ho is silent as any cytotoxic effect of NK cells on trophoblasts that have escaped to maternal circulation.

Plus, POSAs in the nucleic acid detection art knew that fetal cells existed in maternal blood for decades after birth. Bianchi 1996 (EX2010) at 705:2:¶1; 707:1:¶3. This is further evidence that Ariosa's position is unsupportable.

In summary, it was known by March 1997 that fetal trophoblasts in circulation were *not* targets of peripheral NK cells. So, once again, Ariosa fails to establish facts to support its theorized unpatentability grounds.

c) Artisans did *not* believe that all or most cells release DNA into plasma.

Ariosa's Petition also asserted, wrongly, that artisans believed all or most cells release DNA into plasma. This is untrue. By March 1997, it had only been *speculated* that some very small subset of mammalian cells release their DNA into blood under certain, limited conditions. These conditions included some cancers and some auto-immune diseases.

Again, this additional position of Ariosa's is unsupported. First, Ariosa cites portions of the Mansfield Declaration that do not support Ariosa's allegation because they do not discuss anything about cells releasing DNA into the blood. 2nd Pet. at 9-10 (citing EX1047 at ¶85-86). Second, Ariosa cites several articles that do

not support Ariosa's position and that are irrelevant to the field of fetal nucleic acid detection. 2nd Pet. at 10. These articles almost exclusively discuss in vitro data and therefore do not establish that cells release DNA into the bloodstream. EX 1009, throughout; EX 1010 at 3:¶2, 3:¶6 & 8:¶4 (*in vitro* data, e.g., for bacteria, frog hearts and lymphocytes); EX 1028 at 1-17, 39-41 & 44. Likewise, Ariosa relies on (i) data relating to cerebrospinal fluid (i.e., not blood) and (ii) inconsistent, conflicting data relating to lupus. These irrelevant and inconstant data cannot establish that "it was well known that nucleic acids were released into the plasma by cells that circulate in the bloodstream" 2nd Pet. at 11:¶2; EX 1009 at 2375:2:¶2; EX 1028 at 18:¶4.

2. The prior art taught away from using the non-cellular part of maternal blood to detect fetal nucleic acid.

The prior art, as a whole, taught away from the claimed invention.

It took the "outside the box" thinking of Drs. Lo and Wainscoat to arrive at the '540 patent claims. "Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness." MPEP 2145(IX)(3); *In re Hedges*, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). "An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc*., 567 F.3d 1314, 1326 (Fed.

Cir. 2009) (finding that references teaching that increasing rigidity in a spinal pedicle screw will increase the risk of failure teach away from claims reciting a rigid pedicle screw).

Before the '540 patent was filed, skilled artisans exerted significant effort trying to isolate fetal cells from maternal blood to develop non-invasive fetal nucleic acid detection methods. In these attempts, skilled artisans routinely discarded the cell-free portion of the blood and focused their efforts on examining the DNA found in fetal cells. In other words, leading researchers threw away the very material that Drs. Lo and Wainscoat rely upon in their ground-breaking method. Indeed, others had stated that the "maternal serum or plasma [was] ... the waste products of routine diagnostics."). EX2048 at 518:2:¶4 And as Dr. Bianchi stated, in an invited editorial about the significance of the claimed invention: "In the past, the plasma has been discarded," Bianchi 1998 (EX2071) at 763:2:¶2.

The fact that serum and plasma were routinely discarded was a significant reason that the presence of fetal DNA in maternal plasma was not explored and was later deemed the "Holy Grail." EX1016 at 486:1:¶6; EX2071 at 763:2:¶2 (confirming that "[i]n the past, the plasma has been discarded."); EX2015 at 230:2:¶4.

And Dr. Bianchi has also acknowledged that POSAs, before the invention, believed that fetal and maternal circulations were "separated by a generally

impermeable chorionic barrier." EX2071 at 764, ¶4.

Plus, POSAs believed that DNA has high in vivo turnover due to the presence of plasma deoxyribonucleases, and have now recognized that the claimed invention contradicts this belief: "It is somewhat surprising that fetal DNA is not immediately metabolized." EX2079 at 576, ¶2; EX2019 at 198, ¶1 (referring to the presence of DNA degrading deoxyribonucleases in plasma).

Thus, the prior art as a whole directly taught away from the '540 patent's invention.

3. There was no reasonable expectation of successfully detecting fetal nucleic acid in the non-cellular part of maternal blood.

In light of conventional thinking in the art, there was no reasonable expectation of successfully detecting fetal nucleic acid in the non-cellular part of maternal blood: Researchers trying to develop methods for detecting fetal nucleic acid and cancer nucleic acid were highly doubtful that a non-invasive fetal nucleic acid analysis method could be developed.

Researchers attempted to develop non-invasive fetal nucleic acid detection methods based on recovering fetal cells from maternal blood, but discovered that these cells were extraordinarily rare.

- "…all observers agree that fetal cells in maternal blood are rare.";

  EX1025 at 1236:2:¶ 1

- "Fetal cells are extraordinarily rare in maternal blood." EX1011 at 850:2:¶3
- "Also unknown is whether fetal cells are present in the circulation of all pregnant women." EX1011 at 850:1:¶2
- The ratio of nucleated fetal cells to nucleated maternal cells ranged from 1 per 5x106 to 1 per 1x108. Ex. 1025 at 1234:2:¶5 to 1236:1:¶1.

Concerning fetal trophoblasts, artisans viewed them as especially challenging to work with: "Trophoblast, in particular, is notoriously difficult to isolate to a sufficient degree of purity for in vitro experimentation." EX2072 at F226:2:¶2.Sargent taught that most pregnant women do not have trophoblasts in their peripheral circulation. EX2038 at 155:¶3, 159:¶1 (following bullet point text) to 160:¶2. And Simpson 1994 described the many difficulties researchers had encountered in trying to recover trophoblasts from maternal blood. EX1025 at 1230:2:¶2 to 1232:1:2.

And other blood-based nucleic acid detection methods were being explored for cancer, but these methods could only detect a fraction of cancers: "[D]etectable amounts of circulating DNA were found only in [27% of cancer] patients [i.e., those] with advanced malignancies bearing a large tumor cell burden." EX1027 at 711:1:¶1 & 2; EX1019 at 1035:Abstract (29% of patients had detectable microsatellite alterations in cell-free DNA—all having advanced disease). So

these researchers were skeptical that serum contained enough DNA extracted from the cells could be used diagnostically: "[T]here may be problems developing diagnostic and screening tests for early cancer…." EX2040 at 628:2:¶2. Because of these concerns, researchers proposed only using these detection methods *after* initial diagnosis—for, e.g., assessing tumor burden and predicting future metastases. EX1019 at 1035:Abstract & 1037:1:¶3.

Likewise, artisans in prenatal nucleic acid detection repeatedly expressed frustration that there weren't enough fetal nucleated cells in maternal blood to be able to use them as a source for fetal DNA. EX1011at 848:1:¶2, 850:1:2:¶ ¶3-4 &851:1: ¶1; EX1024 at 2359:3:¶5 & 2360:1:¶1; EX1025 at 1237:2:¶5 to 1238:1: ¶1; EX2088 at 1202:1: ¶1.

Because fetal cells were so rare in maternal blood, and because only advanced cancers with heavy tumors loads were detectable using nucleic acid in blood, POSAs in the field of fetal nucleic acid detection would not have had a reasonable expectation of developing a successful method to detect fetal nucleic acid using maternal serum or plasma. Accordingly, Ariosa has failed to establish a *prima facie* case of obviousness.

B. In the unlikely event that Ariosa establishes *prima facie* obviousness, significant objective evidence rebuts the *prima facie* case.

Ariosa has failed, for both factual and legal reasons, to establish *prima facie*

obviousness. But assuming that Ariosa has established a *prima facie* case, Isis provides compelling, objective evidence that warrants finding the '540 patent claims nonobvious: (a) non-invasive nucleic acid detection methods were met with considerable skepticism from experts, and (b) the invention (i) received the praise of others in the field, (ii) satisfied a long-felt and previously unmet need, (iii) achieves unexpected results, (iv) has been copied, and (v) achieved commercial success.

The Federal Circuit has repeatedly stressed the importance of considering objective evidence of nonobviousness: "[T]his evidence is not just a cumulative or confirmatory part of the obviousness calculus but constitutes *independent evidence* of nonobviousness." *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (emphasis added). Record evidence of nonobviousness is probative and must be given substantial weight.

1. Experts and POSAs expressed skepticism about maternal peripheral blood-based nucleic acid detection methods.

Experts and others expressed skepticism about peripheral blood-based nucleic acid detection methods before the '540 patent's priority date.

In Federal Circuit cases containing evidence of skepticism of contemporaries, the court has overwhelmingly determined that such skepticism was sufficient to support the nonobviousness of the invention. For example,

evidence that a "few in the market" were skeptical was sufficient to prove nonobviousness. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc*., 699 F.3d 1340, 1352 (Fed. Cir. 2012). Thus, skepticism of experts is strong evidence of nonobviousness. *Environmental Designs, Ltd. v. Union Oil Co. of Cal*., 713 F.2d 693, 698 (Fed. Cir. 1983).

Since at least 1969, researchers attempted to develop non-invasive fetal nucleic acid detection methods, e.g., based on recovering fetal cells from maternal blood. EX1024 at 2357:2; ¶2 to 3:¶1; EX1025 at 1229:2:¶ 2. But by the 1980s and again in the 1990s, researchers expressed skepticism about the viability of such methods for at least four reasons: (i) fetal cells in maternal blood were rare, (ii) the tools to purify fetal cells from maternal blood had not yet been developed, despite much effort, (iii) not all pregnant women had fetal cells in their blood, and (iv) some fetal cells persisted for decades after birth and blood-based tests were therefore unreliable for testing a subsequent pregnancy.[10]

[10] "…all observers agree that fetal cells in maternal blood are rare." EX1024 at 1236:2:¶ 1; "Fetal cells are extraordinarily rare in maternal blood" and "Also unknown is whether fetal cells are present in the circulation of all pregnant women." EX1011 at 850:2:¶3 & 850:1:¶2; EX2010 at 705:Title & Abstract (male fetal cells were found in maternal blood 27 years after birth).

By March 1997, researchers had repeatedly reported that fetal cells in maternal blood were "extraordinarily rare." EX1011 at 850:2:¶3. Importantly, the ratio of nucleated fetal cells to nucleated maternal cells ranged from 1 per $5x10^6$ to 1 per $1x10^8$. EX1025 at 1234:2:¶5 to 1236:1:¶1. Because of the rarity of these fetal cells, researchers attempted many purification methods. EX1011 at 848:1:¶2 to 851:2:¶1. Specifically, researchers attempted to purify and detect DNA from fetal trophoblasts, fetal lymphocytes, fetal granulocytes, and fetal nucleated red blood cells. *Id*.; EX1024 at 2357:2:¶2 to 2359:1:¶1; EX1025 at 1230:2:¶2 to 1233:1:¶3.

But the rarity of these fetal cells and the inability to develop an adequate purification technique precluded researchers from successfully developing a cell-based fetal nucleic acid detection method. EX2011 at 35:2:¶¶2-3 (the very small number of fetal cells requires fetal cell enrichment but no antibodies had been developed to adequately carry out such enrichment); EX2012 at 649:1:¶1 & 650:¶3 (a 2002 paper describing "sobering" preliminary results using fetal cells enriched using two different platform cell sorting technologies (FACS and MACS)—"neither approach can attain the degree of efficacy necessary for clinical application.").[11] Fetal trophoblasts were especially challenging to work with:

[11] Such post-filing date art may help establish the level of skill in the art at the time of the invention. *See Newell Co., Inc. v. Kenney Mfg. Co*., 864 F.2d 757,

"Trophoblast, in particular, is notoriously difficult to isolate to a sufficient degree of purity for in vitro experimentation." EX2072 at F226:2:¶2.

In short, POSAs were skeptical that a reliable, non-invasive maternal blood-based detection method could be successfully developed for fetal nucleic acid. But once they learned of the claimed invention, they accepted it, as is discussed below.

2. The claimed invention was accepted and praised by others.

Nonobviousness is also supported if POSAs praise the invention. "Appreciation by contemporaries skilled in the field of the invention is a useful indicator of [nonobviousness]." *See Vulcan Eng'g Co. v. Fata Aluminium, Inc.*, 278 F.3d 1366, 1373 (Fed. Cir. 2002). The '540 patent's invention has been recognized with significant praise in the field.

For example, POSAs have praised the invention for overcoming the deficiencies of non-invasive, fetal cell-based nucleic acid detection methods: A lead researcher called the invention "[a] breakthrough." EX2078 at 487:2:¶3. Additional expressions of the praise of contemporaries include:

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766 n.12 (Fed. Cir. 1988) (references that are not "prior art" may be admissible to show the level of skill in the art and may be probative of obviousness) (citing *Thomas & Betts Corp. v. Litton Sys., Inc.*, 720 F.2d 1572, 1580-81 (Fed. Cir. 1983)).

- Researchers in prenatal diagnostics praised the claimed method as having achieved the "Holy Grail" of prenatal diagnosis that "has most prominently influenced the development of new non-invasive alternatives for prenatal diagnosis." EX2015 at 226:1:¶1 & 230:2:¶4; EX2012 at 654:1:¶2.

- POSAs described the claimed method as making non-invasive prenatal diagnostics "a realistic and testable option" and "the first example of real success in [non-invasive prenatal diagnosis]...." EX2008 at 373:1:¶2; EX2015 at 230:2:¶4.

- The Royal Society described the invention as "creating a paradigm shift in non-invasive prenatal diagnostics." EX2042 at ¶2.

- In 2012, Dr. Lo was awarded the Illy Tieste Science Prize in human health for his development of, and continued work on, diagnostics based on cell-free fetal DNA in maternal plasma. EX2043.

In addition, Sequenom's commercially-available tests—the MaterniT21 and MaterniT21 PLUS tests, which embody the '540 patent claims— havereceived substantial praise. For example, Dr. Barbara O'Brien, a physician and director of Perinatal Genetics at Women's & Infants Hospital commended the MaterniT21 test as having "an important place in the plan of care for women who are at a high risk for carrying a child with Down syndrome." EX2046 at ¶3. Likewise, Dr. Frank Boehm, Vice Chairman of the Department of Obstetrics and Gynecology and Director of Maternal Fetal Medicine at Vanderbilt Center for Women's Health, stated that "[a]s part of our mission to provide the *best possible medical care* to patients visiting our facility, we are pleased to provide patients with access to Sequenom CMM's MaterniT21 LDT as an opportunity to gain valuable

information early in a woman's pregnancy." *Id.* at ¶5 (emphasis added).

Importantly, the American College of Obstetricians and Gynecologists (the U.S.'s leading group of physicians providing health care for women) and the Society for Maternal-Fetal Medicine recommend using the MaterniT21 test. EX2047 at, *e.g.*, ¶1.[12]

The acclaim of contemporaries for the '540 patent's claimed method demonstrates a significant, nonobvious advance over the art.

3. The '540 patent satisfied a long-felt, unmet need.

The '540 patent satisfied a long-felt but previously unmet need for a non-invasive fetal nucleic acid detection method. A finding of nonobviousness is supported if the claimed invention satisfies a long-felt need. *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). Demonstrating a long-felt need requires showing that a recognized, persistent, and unfulfilled need existed, and that it was satisfied by the claimed invention. *See In re Gershon*, 372 F.2d 535, 539 (C.C.P.A. 1967.

Prior to the '540 patent's priority date, detecting fetal aneuploidy was performed by amniocentesis and CVS. These methods are invasive and carry risks

[12] Note that the field is "maternal-fetal" medicine, not maternal-embryonic medicine.

for the fetus and mother. EX2015 at 226:2:¶2. Experts long ago expressed a need for a non-invasive method to detect paternally-inherited fetal nucleic acids. *Id*. at 230:2:¶4. Beginning in 1969, researchers actively—but unsuccessfully—pursued non-invasive detection methods by seeking to isolate rare fetal cells from maternal blood. EX1024 at 2357:1; ¶1 to 3:¶2. & 2360:2:¶3 to 3:¶1. This was viewed as such an important need that, in 1987, the National Institute of Child and Human Development began funding the "NIFTY" trials, which involved several research centers. EX1024 at 2360:2:¶3 to 3:¶1.

Despite rigorous efforts, no one achieved acceptable results: "An old and so far unfulfilled dream … is to have a method available which would allow *in utero* diagnosis of genetic anomalies without having to bear procedure-related risks to the mother and/or the fetus." EX2006 at 218:1¶1. The NIFTY trial results were very disappointing. EX2073 at 178:1:¶4 to 2:¶1 (discussing data showing poor low detection and high false-positive rates). After decades of trying to develop a non-invasive method (since 1969), e.g., by using fetal cells, scientists were doubtful as to whether non-invasive fetal cell testing would "ever become available as a clinical routine diagnostic test." EX2048 at 519:2:¶5.

The '540 patent's invention satisfied this long-felt need. It provides reliable, non-invasive fetal nucleic acid detection by amplifying and detecting paternally inherited nucleic acid in maternal serum or plasma. EX2073 at 178:2:¶2. This

technology was first commercialized by Sequenom by 2010 with the SensiGene™ Fetal RHD Genotyping test. More recently, this claimed technology was commercialized again as a fetal aneuploidy detection method, and even though only recently introduced to the commercial marketplace,[13] already greatly reduces the percentage of women who undergo risky invasive testing procedures: "At the Cleveland Clinic, doctors perform 50% fewer invasive procedures." EX2081 at 3:¶6. A recent publication in a peer-reviewed journal co-authored by Dr. Lo predicted an even bigger reduction due to the invention: "If referrals for amniocentesis or [CVS] were based on the sequencing test results [using the '540 patent's claimed method], about 98% of the invasive diagnostic procedures could be avoided." EX2022 at 1:Abstract:Conclusion.

Thus, the inventors on the '540 patent succeeded where others had failed in providing a non-invasive prenatal nucleic acid detection method. As discussed above, the claimed methods have been widely praised and commercially recommended. It thus satisfied a long-felt but previously unmet need.

4. The claimed invention achieves unexpectedly superior reliability than the closest prior art.

The claimed invention achieves unexpected results over prior art attempts to

[13] Sequenom released its first commercial test that embodies the claims by 2010 and its second commercial test that embodies the claims in 2011.

develop a non-invasive fetal nucleic acid detection method. Dr. Bianchi, a prolific author in the prenatal diagnosis field, stated that Drs. Lo' and Wainscoat's method "has the advantage of being rapid, reliable, reproducible, and easily carried out for a large number of samples." EX2018 at S93:2:¶2 to S94:1:¶1.

Others in the field have noted the invention's sensitivity and specificity as being "considerably higher than can be currently attained by the analysis of fetal cells." EX2021 at 864:2:¶1. In the clinical field, this is a keystone improvement.

5. The claimed invention revolutionized the non-invasive prenatal nucleic acid detection field and achieved significant commercial success.

The commercial success of the '540 patent reflects the non-obviousness of the claimed invention. *See, e.g., SIBIA Neurosciences, Inc. v Cadus Pharm. Corp*., 225 F.3d 1349, 1358 (Fed. Cir. 2000). However, commercial success "is relevant in the obviousness context only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). There is a presumption of nexus if the successful commercial embodiment is the claimed invention itself. *Demaco Corp. v. F. Von Langsdorff Licensing Ltd*., 851 F.2d 1387, 1392 (Fed. Cir. 1988).

Here, the claimed invention—a non-invasive method for detecting

paternally-inherited fetal nucleic acid—underlies the commercial acquiescence in the '540 patent and the expanding sales of its commercial embodiments.

Appreciating that claimed method achieved the "Holy Grail" of fetal nucleic acid detection, Sequenom voluntarily entered into an exclusive, royalty-bearing license for the '540 patent and its corresponding patents worldwide. EX2049 at 4:¶5, 5:¶2 & F-27:¶¶1-2. While the exact amount Sequenom paid for this license is confidential, and is still growing with continued sales, it is and will be a substantial payment measured in the millions of dollars. *See id*. The amount paid for a license is significant in determining non-obviousness. *John E. Thropp's Sons' Co. v. Seiberling*, 264 U.S. 320, 330 (1924)). And Sequenom has sub-licensed to LifeCodexx AG and Laboratoire Cerba for upfront and minimum annual royalty payments, the right to the European counterpart of the '540 patent and the right to commercialize non-invasive fetal nucleic acid detection services in Europe. EX2050 at ¶¶1-2; EX2080 at ¶¶1-3. Such success in licensing foreign counterpart patents is to be given weight when determining obviousness. *Continental Can Company USA, Inc. v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991).

Under its exclusive license, Sequenom developed the MaterniT21 test—the first U.S. launched non-invasive nucleic acid detection test for trisomy 21. EX2051 at 440:¶1. This test embodies the claims of the '540 patent. EX2045 at 20459:1:¶2 to 2:¶2 ("One end of the clonally expanded copies of each plasma DNA fragment

was sequenced … to detect chrY DNA from plasma of women carrying male fetuses."). According to genetic-counselors, patients choose the MaterniT21 test over *invasive* prenatal diagnostic tests: "[A]ll patients want to hear that you don't need to have something invasive." EX2081 at 4:¶2. And because Sequenom's MaterniT21 test encompasses the non-invasive prenatal diagnostic methods of the '540 patent, sales have grown every quarter. EX2052 at ¶¶1-2.

More recently, Sequenom developed the MaterniT21 PLUS test, which detects trisomies 13 and 18 and chromosome Y addition to detecting trisomy 21. EX2047 at 2:¶ ¶3-4. And in early 2012, financial analyst Zarak Khurshid predicted that Sequenom would run 40,000 of the tests in 2012. EX2052 at 2:¶3. In fact, sales through September 2012 exceeded expectations, and analysts revised the 2012 estimate to 50,000 tests. EX2053 at slide 6:point 5. With the expectation of an increasing market demand, Sequenom has increased its run rate to 90,000 per year. *Id.* at slide 20:point 5.

In sum, substantial licensing fees for the '540 patent family and the current and predicted increasing demand for Sequenom's tests are strong evidence of the nonobviousness of the claimed invention.

6. The '540 patent has been copied.

In addition to all of the significant evidence discussed above, the '540 patent has been copied by no fewer than three companies and numerous researchers.

Ariosa, Natera, and Verinata all practice the claimed invention. *See e.g.*, EX2003 at 3:¶10; EX2083at 3:¶13; EX2085 at 4:¶18; EX2086 at 15:¶25. Plus, many publications confirm that others in the field also use the invention. *See e.g.*, EX2012 at 654:1:4 & 654:2:3; EX2015 at 228:Table1; EX2018 at S99:2:¶1. These are two more data point showing, objectively, that the claimed invention was nonobvious.

7. The objective evidence has a nexus to the merits of the claimed invention.

A nexus exists between this objective evidence of nonobviousness and the merits of the '540 patent claims because the praise and commercial success are directly due to the invention's merits over the prior art. POSAs praise the claimed invention because it reliably achieves non-invasive detection of paternally inherited nucleic acid of fetal origin using maternal serum or plasma: "[A]ll patients want to hear that you don't need to have something invasive." EX2081 at 4:¶2. And the substantial licensing fees paid for the '540 patent family reflect the perceived value of a non-invasive test for detecting fetal nucleic acid. Likewise, Sequenom's commercial tests embody the '540 patent claims and reflect the merits of the claimed invention: they amplify and detect paternally-inherited fetal nucleic acid in maternal plasma or serum samples in a noninvasive way.

C. Ariosa is not reasonably likely to prevail on its proposed Ground B.

Ariosa is not reasonably likely to prevail on its proposed Ground B. Claims 3, 12, 13, 15, and 18 are nonobvious over Kazakov in view of Mutter because of the reasons discussed in detail above: (a) Ariosa has not established a prima facie case, (b) the prior art as a whole taught away, and (c) substantial objective evidence shows the claims were nonobvious.

D. Ariosa is not reasonably likely to prevail on its proposed Grounds C-F.

Ariosa is not reasonably likely to prevail on its proposed Grounds C-F. As is discussed above, the '540 patent is entitled to its GB application's priority date of March 4, 1997, thus removing Lo 1997 (published in August 1997) and Schallhammer (published in July 1997) as prior art. EX2035 (date stamp). Removal of Lo 1997 renders defective proposed Grounds C and D, and removal of Schallhammer renders defective proposed Grounds E and F.

And for the additional reasons discussed above in Section VI, claims 3, 12, 13, 15, and 18 are nonobvious over Simpson in view of Schallhammer, Kazakov and Bianchi (proposed Ground E), and they are nonobvious over Simpson in view of Schallhammer, Kazakov and Mutter (proposed Ground F).

E. Ariosa is not reasonably likely to prevail on its proposed Ground G.

Ariosa is not reasonably likely to prevail on its proposed Ground G.

Kazakov does not anticipate claim 8 for the reasons discussed above in Section IV.

VII. This IPR is barred.

A. *Inter partes* review may not be instituted because Ariosa was served with a complaint alleging patent infringement over one year ago.

The Office may not institute *inter partes* review if the petitioner filed its petition more than one year after being served with a complaint alleging infringement of the patent. 35 U.S.C. § 315(b). On January 24, 2012, Aria Diagnostics, Inc. (now "Ariosa") accepted service of a complaint alleging infringement of the '540. EX2083; EX2084. As such, the Office is barred by statute from instituting the in*ter partes* review requested by Ariosa over one year later on April 19, 2013.

Although the parties later agreed to a dismissal of the civil action without prejudice, the plain language of the statute makes no exception for such an event: *inter partes* review "may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner. . . is served with [the] complaint." 35 U.S.C. § 315(b). This statute leaves no room for agency discretion. Because the complaint here was served on Ariosa more than one year before Ariosa filed the instant petition, the Office may not institute *inter partes* review.

In a specific context, that of subsequently filed litigation, a prior litigation

that is voluntarily dismissed without prejudice "renders the proceedings a nullity" and "leaves the parties as though the action had never been filed." E.g., *Graves v. Principi*, 294 F.3d 1350, 1356 (Fed. Cir. 2002) (statute of limitations is not tolled by a notice of appeal if the appeal is voluntarily dismissed without prejudice); *see also Bonneville Assocs. Ltd. P'ship v. Barram*, 165 F.3d 1360, 1364 (Fed. Cir. 1999). Thus, in this context, a voluntary dismissal without prejudice makes any future lawsuit based on the same claim a "new" lawsuit to the dismissed action. *Sandstrom v. Chemlawn Corp*., 904 F.2d 83, 86 (1st Cir. 1990). Thus, just as a voluntarily dismissed action does not toll the statute of limitations, *Graves*, 294 F.3d at 1356, an alleged consent to jurisdiction does not carry from one case to the next. *Sandstrom*, 904 F.2d at 86.

But this general rule has exceptions. For example, the "two dismissal rule" prevents harassing a defendant by repeatedly filing complaints and dismissing them without prejudice. E.g., *Engelhardt v. Bell & Howell Co*., 299 F. 2d 480, 482 (8th Cir. 1962). This would not be the case if the parties were truly left as if the first suit had never been filed. Similarly, a court may still impose sanctions for conduct that occurred during a proceeding which was voluntarily dismissed without prejudice. *Sandstrom*, 904 F.2d at 87 n.4. The dismissed procedure was not truly rendered a nullity, as the misconduct still exists.

Likewise, the previous existence of a civil action may trigger a statutory bar

to another proceeding, even if the civil action was voluntarily dismissed without prejudice. For example, the Vaccine Act forbids the Court of Federal Claims (CFC) from entertaining a petition when there is a co-pending civil action. But voluntarily dismissing the civil action without prejudice does not render the civil action a nullity as to the statutory bar. *Flowers v. HHS*, 49 F.3d 1558 (Fed. Cir. 1995). In Flowers, the petitioner filed her civil action in court and then filed her petition at the CFC. *Id*. at 1559. After learning that the Vaccine Act did not allow co-pending actions, the petitioner voluntarily dismissed her civil action without prejudice. *Id*. The civil action was not rendered a nullity so far as the Vaccine Act's statutory bar was concerned. On the contrary, the Federal Circuit held that the CFC was required by statute to dismiss for lack of jurisdiction even though the civil action was voluntarily dismissed without prejudice. *Id*. at 1559, 1562.

As with the "two dismissal rule" and the Vaccine Act's statutory bar, that Sequenom's infringement suit was later dismissed voluntarily without prejudice does not affect § 315(b)'s statutory bar. Because Ariosa was served with a complaint alleging infringement of the patent over one year before it filed this petition, the Office is barred from instituting *inter partes* review.

B. Title 35 of the United States Code has no provision for the "joinder" of additional arguments, only additional parties.

Under Section 315(b), the Office may not institute inter parties review if the

petitioner was served with a complaint over one year ago unless the petitioner seeks to join an existing proceeding. But the § 315(c) exception addresses only the joinder of a *party*, not the "joinder" of additional grounds from the same party:

> JOINDER -- If the Director institutes an inter partes review, the Director . . . may join *as a party* to that inter partes review *any person* who properly files a petition under section 311.

Here, Ariosa cannot be "joined" as a party to its own *inter partes* review because it is already a party. The plain meaning of "joinder" is to join *persons*, not *arguments*, to a proceeding. *See, e.g.*, Fed. R. Civ. P. 20 ("Permissive Joinder of Parties"). The Director's authority to consolidate proceedings involving the same petitioner derives from § 325(d), not § 315(c).

Congress meant what it said when it enacted the joinder exception. As Senator Kyl explained, the joinder exception is intended to allow "a *party* that files an identical petition [to] be joined to that proceeding, and . . . file its own briefs and make its own arguments." EX2074 at S1376:1:¶2. (emphasis added). Similarly, "[i]f a *party* seeking joinder also presents additional challenges to validity that satisfy the threshold for instituting a proceeding," then that *party* may joined to present its additional arguments. *Id*. (emphasis added).

The AIA created *inter partes* review as a cost-effective alternative to litigation, not as an additional tool to be used to serially challenge patents during

litigation. The legislative history of 35 U.S.C. § 315(b) shows that the one-year time period was meant to provide defendants sufficient time to fully analyze the patent claims, it was not meant to create an open-ended process. *See* EX2075 at S5429:3:¶1; *see also* EX2076 at 72:¶2 ("The inter partes proceeding in H.R. 1249 has been carefully written to balance the need to encourage its use while at the same time preventing the serial harassment of patent holders"). It did not create the joinder exception to give petitioners a "do-over."

Ariosa has already had its one-year period to "fully analyze the patent claims." Allowing Ariosa to "join" its additional arguments to its own *inter partes* review would contravene the plain language of the statute and thwart Congressional intent by "creating an open-ended process." Accordingly, Ariosa cannot be joined to its own *inter partes* review. As a result, the exception to § 315(b)'s statutory bar for joinder does not apply here.[14]

[14] The Board has not yet authorized Isis to file an opposition on the merits to Ariosa's motion for joinder and, thus, such arguments are omitted here. Should the Board apply the joinder exception now, a later finding that joinder was not warranted on the merits will remove the joinder exception and thus bar Ariosa's requested review under §315(b).

D. Even if the Director grants Ariosa's petition, trial should not be instituted on claim 8.

In IPR 2012-0022, the Board denied Ariosa's petition with respect to Ariosa's contention that claim 8 is anticipated by the Kazakov reference. EX1042 at 37:¶8. Undeterred, Ariosa once again argues that Kazakov anticipates claim 8 for substantially the same reasons as previously argued.

Section 325(d), however, gives the Board the discretion to "take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office." Congress enacted § 325(d) to "prevent parties from mounting attacks on patents that raise issues that are substantially the same as issues that were already before the Office with respect to the patent." EX2074 at S1376:1:¶3 .

During rulemaking, the Office therefore explained that the Board "will exercise its authority under 35 U.S.C. § 325(d), where appropriate, to deny petitions that submit the same or substantially the same prior art or arguments previously presented to the Office." EX2077 at 48702:1:¶7.

With respect to claim 8, Ariosa's new petition submits the same prior art (Kazakov) *and* makes substantially the same argument (inherent anticipation). Accordingly, the Board should deny Ariosa's petition as to claim 8.

C. *Inter partes* review should not be instituted because Ariosa previously filed a civil action challenging validity.

The Office may not institute *inter partes* review if the petitioner or real party in interest previously filed a civil action challenging the validity of the patent. 35 U.S.C. § 315(a)(1). On December 19, 2011, Ariosa filed a civil action against Sequenom in U.S. District Court for the Northern District of California, seeking a declaratory judgment of noninfringement. EX2002 at 1.[15] Sequenom counterclaimed for infringement, and Ariosa raised the affirmative defense of invalidity in its answer. EX2004 at 4:6-9. As such, § 315(a)(1) bars instituting the *inter partes* review requested by Ariosa.

The Board's previous decision in IPR2012-0022 notwithstanding, § 315(a)(1) expressly forbids instituting Ariosa's *inter partes* review. The plain text of the statute and the legislative history show that Congress enacted this statutory bar to avoid patent owner harassment and to provide a cost-effective alternative to district court litigation. *See, e.g.*, EX2005 at S952:1:6 (statement of Sen. Chuck Grassley) ("[The IPR statute] would establish an adversarial *inter partes* review, with . . . procedural safeguards to prevent a challenger from using the process to harass patent owners."); *Id*. at S951:2:2 (statement of Sen. Orrin Hatch) ("The bill

[15] Aria Diagnostics, Inc. is the named party in that action. Aria later changed its name to Ariosa.

will . . . creat[e] a cost-effective alternative to formal litigation, which will further enhance our patent system.").

VIII. Conclusion

The Board should not institute *inter partes* review because Ariosa has not met its burden to show it has a reasonable likelihood of prevailing on any of its proposed grounds of unpatentability. Additionally, the petition should be denied because Ariosa lacks standing to petition for IPR in view of (i) its prior district-court challenge to the validity of the '540 patent and (ii) the fact that Ariosa was served with a complaint alleging infringement of the '540 patent more than a year ago. And even if the Board institutes review, Ariosa's proposed grounds of unpatentability against claim 8 should be denied because the same art and arguments previously were presented to the Office. If the Board institutes IPR, Isis Innovation reserves the right to supplement its arguments as to why Ariosa will not prevail on the merits of its unpatentability challenge.

The Patent Trial and Appeal Board is hereby authorized to charge any fees associated with the *inter partes* review no. 2012-00250 to Deposit Account 19-0036. Our Customer I.D. is 45324.

Respectfully submitted,
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Date: June 10, 2013

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IX. CERTIFICATION OF SERVICE (37 C.F.R. §§ 42.6(e))

The undersigned hereby certifies that the above-captioned "Isis Innovation Limited's Preliminary Response," was served in its entirety on June 10, 2013, upon the following parties via FedEx®:

Greg Gardella
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